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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,901	04/13/2005	Toshiyoshi Fujiwara	09857/0202272-US0	2780

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,901	FUJIWARA ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 14, 2008 has been entered.

Claims 4-11 are pending. Claims 4, 8, and 11 are amended. Claims 4-11 are currently under examination.

Priority

2. This application 10/520,901 is a 371 of PCT/JP03/08573 07/07/2003 claims the foreign priority of JAPAN 2002-198941 filed on 07/08/2002. A certified copy of the English translation of JAPAN 2002-198941 filed on 07/08/2002 was provided on 09/14/2007 for instant application. The certified copy of the English translation of JAPAN 2002-198941 filed on 07/08/2002 has been considered, and the support for claimed subject matter of instant application can be found in JAPAN 2002-198941. Therefore, the priority date of instant application has been determined to be 07/08/2002, the filing date of JAPAN 2002-198941.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Previous rejection of claims 4-11 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of causing cytotoxicity in cancer cells comprising injection, *in vitro* or *in situ*, of a vector into a tumor comprising said cancer cells, said vector comprising the hTERT promoter operably linked to a polynucleotide comprising a gene encoding adenovirus E1A followed by an IRES and a gene encoding E1B, and for said nucleic acid, does not reasonably provide enablement for 1) a method of treating cancer *in vivo*, or 2) use of the claimed nucleic acid wherein the E1 gene is not operably linked to a promoter to cause expression, is ***withdrawn*** because Applicant's arguments in combination with claim amendments have been fully considered and found persuasive.

With respect to enablement for a method of treating cancer *in vivo*, Applicants argues that that in contrast to the Examiner's characterization, Example 6 describes the administration of a vector (TRAD) construct encompassed by the pending claims to subcutaneously transplanted lung and large bowel cancer cells in nude mice. Applicant argues that the anticancer activity observed in Example 6, compared to a control vector (Ad-p53) that contained no inserted gene (i.e., d1312), is attributable to the injection of a vector encompassed by the claimed methods. The TRAD vector kills cells by replication. In contrast, the control Ad-p53 vector kills cells by expressing the therapeutic gene p53 (See Example 6 and Figs. 8-9). In other words, Ad- p53 is a control vector used to compare with TRAD.

Furthermore, Applicant argues that the test for enablement "is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the

specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed." In re Wands, 858, F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (quoting In re Angstadt, 537 F.2d 489, 502-4, 190 USPQ 214, 217-19) (CCPA 1976)); MPEP § 2164.01. Applicant argues again, that as described in Example 6 is a working example wherein vectors containing the claimed cassette were injected into tumors, thereby killing tumor cells, and this is an *in vivo* example utilizing an exemplary vector construct. Thus, Applicant argues that the specification provides adequate guidance for a person of ordinary skill in the art to make and use the claimed invention both *in vitro*, and *in vivo*.

Applicant argues that there are many *in vitro* assays that have been extrapolated for use in human diagnostic assays or treatments. There are many examples of such assays - notably the *in vitro* assays using Tamoxifen® in MCF-7 cells that have been successfully applied not just to human diagnostic methods, but for treatment of human breast cancer. See for example, *Curr. Opin. Obstet. Gynecol.* 2003 Feb, 15 (1):13-23 (listed in the Information Disclosure Statement of Feb. 23, 2005), "as a prototype for the development of selective estrogen receptor modulators at the laboratory-clinical interface." (*Id.* at page 13, second full paragraph).

Applicant argues that, in any event, *in vivo* data using the claimed vectors is not necessary in order to comply with the enablement requirements of 35 U.S.C. § 112, first paragraph. Courts have consistently and repeatedly held that in vitro activity is sufficient to satisfy the "how to use" portion of the enablement requirement of U.S. patent law.

Finally, Applicant argues that MPEP § 2164.02 discusses correlation of *in vitro* and *in vivo* animal model assays and a disclosed or claimed method of use, and importantly, correlation depends upon the state of the prior art in view of whether a particular model is recognized as

correlating to a specific condition. Applicant argues that MPEP § 2164.02 further states that "even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition." Thus, Applicant states that the nude mouse model for killing tumor cells described in Example 4 (*in vitro*), and the results of injecting the nude mice with a vector construct, fully enable claims 4-11.

The Examiner notes that, upon further consideration, Example 6 of specification provides sufficient information to overcome the first aspect of the rejection on the application of claimed method for killing cancer *in vivo* by administration of claimed polynucleotide cassette. It is worth noting that the administration route used in Example 6 is intratumoral injection of claimed polynucleotide cassette. However, the Examiner cannot find support in the literature that other administration routes will not work because the recombinant virus can spread to various tissues through intravenous administration. Furthermore, as Applicant has argued that no therapeutic gene is required to achieve cancer killing effect. The second aspect of the rejection is withdrawn because claim 4 has been amended to recite hTERT promoter operably linked with E1A-IRES-E1B cassette.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 4-8 and 11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Morin et al.** (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) in view of **Li et al.** (Li et al., A hepatocellular carcinoma-specific adenovirus variant, CV890, eliminates distant human liver tumors in combination with doxorubicin. *Cancer Res.* 61(17): 6428-36, 2001; this reference is disclosed in IDS filed on 04/25/2006, listed as reference CC). Previous rejection is ***maintained*** for the reasons of record advanced on pages 12-14 of the Non-Final office action mailed on 06/19/06.

As set forth at pages 12-14 of the Non-Final office action mailed on 06/19/06, Morin et al., 2000 disclosed use of the hTERT promoter to selectively direct expression in cancer cells. More specifically, Morin et al., 2000 taught oncolytic viruses, in which a toxin or a genetic element essential for viral replication is placed under control of the TERT promoter. Thereby, the virus that replicates preferentially in cells expressing TERT, and thereby selectively lyses cancer cells (See *in vitro* Example 4 on transfected human cell lines, pages 35-36, and *in situ* Example 3 on transplanted human tumor 143B cells on nude mice, page 35, Morin et al., 2000).

While Morin et al. do not teach an adenovirus with IRES inserted between E1A and E1B in an adenovirus as recited in claim 4 of instant application, operably linked to the hTERT promoter, Li taught an adenoviral construct comprising promoter AFP (a-Fetoprotein, a hepatocyte specific promoter) operably linked to E1A-IRES-E1Bto cause efficient replication and destruction of hepatocarcinoma cells.

Therefore, it would have been obvious to combine the teachings of Morin et al., with the teachings of Li et al. to arrive at the claimed vector and methods for killing cancer cells

Applicant argues that Morin does not teach E1A-IRES-E1B. In response, Morin is not relied upon for these teachings. Morin is relied upon for teaching selective tumor cell expression using the hTERT promoter.

Applicant argues there is no motivation to combine the references. In response, Li taught the effective nature of the bicistronic E1A-IRES-E1B cassette under control of hepatocyte specific promoter in killing liver cancer cells. However, the promoter used by Li is not optimal for killing cancer cells in general because promoter AFP (a-Fetoprotein) is a hepatocyte specific promoter.

Applicant argues that the claimed polynucleotide results in unexpected and advantageous effects that would not have been predicted by a person of ordinary skill in the art (see Remarks at page 9). Applicant argues that Li taught adenoviruses that replicate in specific types of cancer while, in contrast the claimed virus can be used in a variety of different cancer cell types. In response, Applicant has failed to point out what result obtained is unexpected. Use of the hTERT promoter, taught by Morin et al. to be expressed in multiple cancer cell types, would be expected to lead to expression in a broader class of cancer than the more hepatocyte specific promoter AFP of Li.

At page 9, Applicant argues Mizuguchi et al. teaches that IRES-dependent second gene expression is less efficient that cap-dependent first gene expression and that a skilled artisan would expect there to not be sufficient E1B expression under the control of an IRES . In response, the Examiner notes that Mizuguchi et al. only provides a general statement regarding

the relative expression levels of genes under IRES translational control. There are no specific teachings in Mizuguchi et al. that are relevant to the claimed polynulcoetide cassette of instant application in terms of whether the expression of E1A and E1B has to be at the same level from the claimed cassette to arrive at the claimed cancer cell killing effect of the poplynucleotide cassette, when administered. Applicant has provided no specific reason to doubt that the level of E1B expression of the claimed construct would be insufficient to lead to viral replication requred for killing cancer cells.

With regard to the asserted requirement for teaching, suggestion, or motivation to render obviousness, the Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner also notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Morin et al. 2000 and Li et al., 2001 has been clearly set forth on pages 12-14 of the Non-Final office action mailed on 03/05/2007, and in this office action as well.

5. Claims 4, 5, 8, 9, and 10 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over **Morin et al.** (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) in view

of **Li et al.** (Li et al., A hepatocellular carcinoma-specific adenovirus variant, CV890, eliminates distant human liver tumors in combination with doxorubicin. *Cancer Res.* 61(17): 6428-36, 2001; this reference is disclosed in IDS filed on 04/25/2006, listed as reference CC) as applied to claims 1-8 and 10 above, and further in view of **Cheng et al.** (Cheng et al., U.S. patent application No. 2003/0104625, publication date, June 5, 2003; filed Feb. 22, 2002; this reference is cited in the office action dated 06/19/2007)

The teachings Morin et al. and Li et al. have been discussed in the preceding section of the rejection of claims 1-8 and 10 under 35 U.S.C. 103(a) as being unpatentable over Morin et al. in view of Li et al.

None of Morin et al. and Li et al. teaches various cancer recited in claim 9 and ostesarcoma and brain tumor recited in claim 10 of instant application.

However, at the time of filing of instant application, treating a type of cancer cell *in vitro* using adenovirus as an anticancer agent (claims 9 and 10 of instant applicant) was known in the art. For instant, Cheng et al. teach tumor and normal tissues, including liver, kidney, lung, bone marrow, brain, spleen, and ovary, were collected from various experimental mice groups, which was administered with adenoviral vector (See paragraph [0570], Cheng et al., 2003).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Cheng et al. regarding treating various cancer cells using adenovirus as an anticancer with the combined teachings of Morin et al. and Li et al. regarding administration of polynucleotide comprising E1A-IRES-E1B cassette expressed under the control of hTERT promoter for lysis of cancer cells to arrive at the method of killing brain cancer cells *in vitro* comprising the step of administering recombinant virus comprising

polynucleotide E1A-IRES-E1B cassette expressed via the control of hTERT promoter, as recited in claims 9 and 10 of instant application.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Cheng et al. regarding treating various cancer cells with adenovirus with the combined teachings of Morin et al. and Li et al. regarding administration of polynucleotide comprising E1A-IRES-E1B cassette expressed via the control of hTERT promoter for killing cancer cells because Morin et al teaches the activity of hTERT promoter is highly specific for cancer cells, which includes brain cancer cells taught by Change et al.

There would have been a reasonable expectation of success given (i) successful demonstration of expression of E1A-IRES-E1B cassette under both transcriptional control of human TERT promoter, by the teachings of Morin et al, and translational control, by the teachings of Li et al for killing cancer cells, and (ii) the demonstration of hTERT promoter control the transcription of adenovirus E4 gene by Cheng et al. (See Fig, 49, Change et al.)

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

6. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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